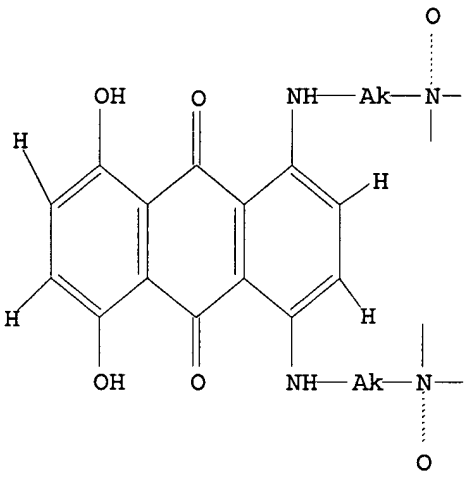
```
=> d his

     (FILE 'HOME' ENTERED AT 10:23:37 ON 29 NOV 2005)

     FILE 'REGISTRY' ENTERED AT 10:23:42 ON 29 NOV 2005
L1                STRUCTURE UPLOADED
L2              0 S L1
L3             18 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 10:24:22 ON 29 NOV 2005
L4             31 S L3

=> d que l4 stat
L1                STR
```



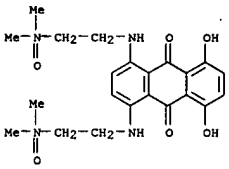

```
Structure attributes must be viewed using STN Express query preparation.
L3             18 SEA FILE=REGISTRY SSS FUL L1
L4             31 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3


=> d 1-31 bib abs hitstr
```

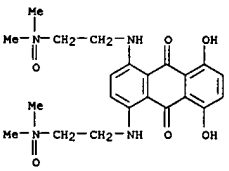
L4 ANSWER 1 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:962193 CAPLUS
DN 143:266690
TI Condensation and amine oxidation process for the preparation of AQ4N
IN Matthews, Ian Timothy William; Scott, Ronald Michael; Barry, John Francis;
Hughes, Stephen William; Heslip, Ann
PA Kudos Pharmaceuticals Limited, UK
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005080314	A2	20050901	WO 2005-GB496	20050211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI US 2004-544778P	P	20040213		

AB AQ4N or its salts (e.g., AQ4N dihydrochloride) are prepared by: the amine oxidation of 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione with a peracid or a peracid salt (e.g., magnesium monoperoxyphthalate) at ≤10°.
IT **136470-65-0P**, Aq4n
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(condensation and amine oxidation process for the preparation of AQ4N)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



L4 ANSWER 2 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:862893 CAPLUS
DN 143:415707
TI A cytochrome P450 2B6 meditated gene therapy strategy to enhance the effects of radiation or cyclophosphamide when combined with the bioreductive drug AQ4N
AU McErlane, Verna; Yakkundi, Anita; McCarthy, Helen O.; Hughes, Ciara M.; Patterson, Laurence H.; Hirst, David G.; Robson, Tracy; McKeown, Stephanie
R.
CS Radiation Science Research Group, School of Biomedical Sciences, University of Ulster, Coleraine, Co. Londonderry, BT52 1SA, UK
SO Journal of Gene Medicine (2005), 7(7), 851-859
CODEN: JGMEFG; ISSN: 1099-498X
PB John Wiley & Sons Ltd.
DT Journal
LA English
AB Background: AQ4N is metabolized in hypoxic cells by cytochrome P450s (CYPs) to the cytotoxin AQ4. Most solid tumors are known to contain regions of hypoxia whereas levels of CYPs have been found to vary considerably. Enhancement of GYP levels may be obtained using gene-directed enzyme prodrug therapy (GDEPT). We have therefore examined the potential of a CYP2B6-mediated GDEPT strategy to enhance the anti-tumor effect of the combination of AQ4N with radiation or cyclophosphamide (CPA). Methods: In vitro and in vivo transient transfection of human CYP2B6 ± CYP reductase (CYPRED) was investigated in RIF-1 mouse tumors. Efficacy in vitro was assessed using the alkaline comet assay (ACA). In vivo, the time to reach 4x the treatment volume (quadrupling time; VQT) was used as the end point. Results: When CYP2B6 was transfected into RIF-1 cells and treated with AQ4N under hypoxic conditions there was a significant increase in DNA damage (measured by the ACA) compared with non-transfected cells. In vivo, a single intra-tumoral injection of a CYP2B6 vector construct significantly enhanced tumor growth delay in combination with AQ4N (100 mg/kg) and 10 Gy X-rays. AQ4N (100 mg/kg) and CPA (100 mg/kg) with CYP2B6 and CYPRED also enhanced tumor growth delay; this effect became significant when the schedule was repeated 14 days later (p = 0.0197). Conclusions: The results show the efficacy of a CYP2B6-mediated GDEPT strategy for bioredn. of AQ4N; this may offer an addnl. approach to target radiation- and chemo-resistant hypoxic tumors that should enhance overall tumor control.
IT **136470-65-0**, AQ4N
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human cytochrome P 450 2B6 gene directed enzyme prodrug therapy enhanced antitumor effects of bioreductive drug AQ4N combined with radiation or cyclophosphamide in RIF-1 fibrosarcoma cells line and in injected mouse)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:588893 CAPLUS
DN 143:115360
TI A preparation of anthraquinone derivatives, useful as antitumor agents
IN Patterson, Laurence Hylton; Pors, Klaus; Teesdale-Spittle, Paul Henry
PA School of Pharmacy, University of London, UK
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

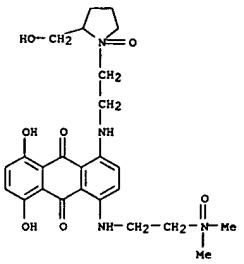
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005061453	A1	20050707	WO 2004-GB5390	20041222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI GB 2003-29820	A	20031223		
GB 2003-30011	A	20031224		

OS MARPAT 143:115360
GI

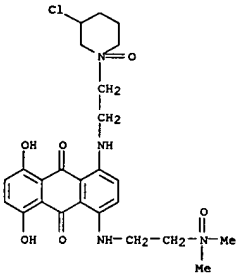
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of anthraquinone derivs. of formula I
{wherein: R1 to R4 are each selected from H, alkyl, halogen, NH-alkanediyl-heterocycle, or OH, etc.}, useful as antitumor agents. For instance, anthraquinone derivative II (inhibition of cell growth: IC50 = 8.4 nM) was prepared via amination of fluoroanthracene derivative III by [1-(2-aminoethyl)piperidin-3-yl]methanol with a yield of 68%.
IT **857637-53-7P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of anthraquinone derivs. useful as antitumor agents)
RN 857637-53-7 CAPLUS
CN 9,10-Anthracenedione, 1-[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-4-[[2-[2-(hydroxymethyl)-1-oxido-1-pyrrolidinyl]ethyl]amino]- (9CI) (CA INDEX NAME)

L4 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



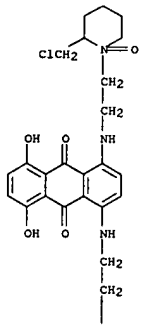
IT 857637-54-8P 857637-55-9P 857637-56-0P
857637-57-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anthraquinone derivs. useful as antitumor agents)
RN 857637-54-8 CAPLUS
CN 9,10-Anthracenedione,
1-[[2-(3-chloro-1-oxido-1-piperidinyl)ethyl]amino]-4-
[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



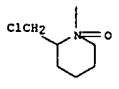
RN 857637-55-9 CAPLUS

L4 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN 9,10-Anthracenedione, 1,4-bis[[2-[2-(chloromethyl)-1-oxido-1-piperidinyl]ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

PAGE 1-A

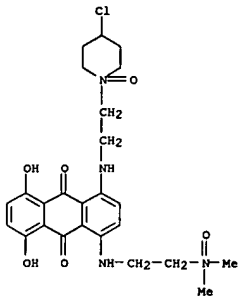


PAGE 2-A

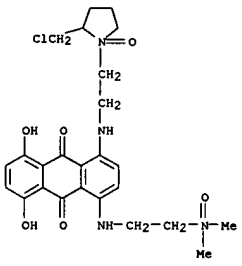


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN 9,10-Anthracenedione,
1-[[2-(4-chloro-1-oxido-1-piperidinyl)ethyl]amino]-4-
[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

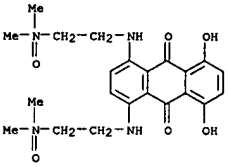


RN 857637-56-0 CAPLUS
CN 9,10-Anthracenedione, 1-[[2-[2-(chloromethyl)-1-oxido-1-pyrrolidinyl]ethyl]amino]-4-[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



RN 857637-57-1 CAPLUS

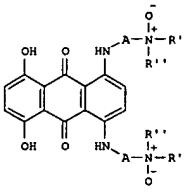
L4 ANSWER 4 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:273838 CAPLUS
DN 142:403302
TI Progress of studies on the inhibitors of topoisomerase
AU Wang, Gang; Wan, Zong-ming; Liu, Yan-qing; Chen, Hong
CS Training Dep., Medical College For Armed Police, Tiajin, 300162, Peop. Rep. China
SO Wujing Yixueyuan Xuebao (2004), 13(3), 260-262
CODEN: WYXUA9; ISSN: 1008-5041
PB Wujing Yixueyuan Xuebao Bianjibu
DT Journal; General Review
LA Chinese
AB A review with 15 refs. summarized recent progress of studies on the inhibitors of topoisomerase including topics of inhibitors of topoisomerase I and II, new drug discovery, and conclusion.
IT 136470-65-0, AQ4N
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(progress of studies on inhibitors of topoisomerase)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:259849 CAPLUS
DN 142:322713
TI Formulations of anthraquinone derivatives
IN Halbert, Gavin William; Ford, Steven John; Elliott, Moira Alexandra
PA BTG International Limited, UK
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005025537	A1	20050324	WO 2004-GB3954	20040916
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI	GB 2003-21787	A	20030917		
	GB 2003-29875	A	20031223		

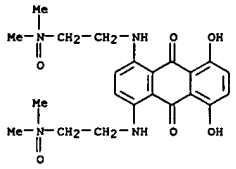
OS MARPAT 142:322713
GI



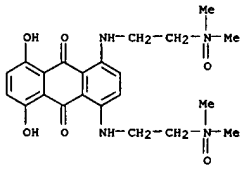
I

AB A stable, sterile aqueous solution of a compound (I, where A is a C alkylene group with a chain length between NH and N(O)R'R' of at least 2 carbon atoms and R' and R' are each sep. selected from C1-4 alkyl and C2-4 hydroxyalkyl and C2-4 dihydroxyalkyl, or R' and R' together are a C2-6 alkylene), is formulated in a unit dosage form in a sealed container, the solution having a

L4 ANSWER 5 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
concn. of 1 up to 150 mg/mL and a pH in the range of 5-9. The soln. may be prepd. without a freeze drying step. Formulations of AQ4N were prepd. at 40 mg/mL in 10 mM sodium phosphate buffer at pH 7.0. Effects of freeze drying on the quality of AQ4N product were studied.
IT 136470-65-0, AQ4N 252979-56-9, AQ4N dihydrochloride
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulations of anthraquinone derivs.)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



RN 252979-56-9 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, dihydrochloride (9CI) (CA INDEX NAME)



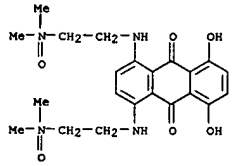
●2 HCl

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:857343 CAPLUS
DN 141:355342
TI Hypoxia-activated prodrugs for treating cancer
IN Matteucci, Mark; Rao, Photon; Duan, Jian-Xin
PA Threshold Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

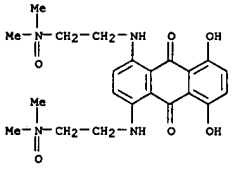
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004087075	A2	20041014	WO 2004-US9667	20040329
	WO 2004087075	A3	20050324		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2520000	AA	20041014	CA 2004-2520000	20040329
PRAI	US 2003-458845P	P	20030328		
	US 2003-465281P	P	20030421		
	WO 2004-US9667	W	20040329		

OS MARPAT 141:355342
AB Hypoxia-activated prodrugs can be used to treat cancer when administered alone or in combination with 1 or more anti-neoplastic agents. Thus, 10-hydroxycamptothecin was treated with N1-methyl-2-nitro-5-(bromomethyl)imidazole to give a prodrug. The prodrug released the active constituent under hypoxic conditions.
IT 136470-65-0D, AQ4N, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoxia-activated prodrugs for treating cancer)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



IT 136470-65-0, AQ4N

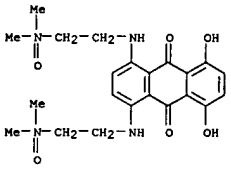
L4 ANSWER 6 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoxia-activated prodrugs for treating cancer)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



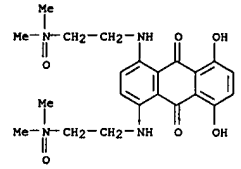
L4 ANSWER 7 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:971708 CAPLUS
DN 140:23217
TI Modulation of tumor cells using BER inhibitors in combination with a sensitizing agent and DSBR inhibitors
IN Zarling, David A.; Reddy, Gurucharan; Taverna, Pietro
PA Pangene Corporation, USA
SO U.S. Pat. Appl. Publ., 22 pp., which
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003229004	A1	20031211	US 2003-394431	20030320
PRAI US 2002-367447P	P	20020320		
US 2003-448732P	P	20030221		

AB The invention relates to methods and compns. for inhibiting the proliferation of cells and sensitizing cells to radiation therapy and DNA damaging chemotherapeutics, and, in particular, treating cancer cells and individuals in vivo, including intra-operative treatments, by administration of a combination of DNA chemo- or radio-sensitizing drugs, BER (DNA base excision repair) pathway inhibitors and DSBR (DNA double strand break repair) pathway inhibitors. Several examples are provided showing that the BER inhibitor methoxyamine increases sensitivity of tumor cells to IUDR, iodouridine-containing oligonucleotides, and fludarabine. Rad51 antisense oligonucleotide, methoxyamine and either doxorubicin or IPDR may also be useful combination in cancer treatment.
IT **136470-65-0**, AQ4N
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor combination of DNA repair inhibitors with sensitizing agents)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



L4 ANSWER 8 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:901484 CAPLUS
DN 140:187538
TI Use of mathematical derivatives (time-domain differentiation) on chromatographic data to enhance the detection and quantification of an unknown rider' peak
AU Ford, S. J.; Elliott, M. A.; Halbert, G. W.
CS Department of Pharmaceutical Sciences, Cancer Research UK Formulation Unit, University of Strathclyde, Glasgow, G1 1XW, UK
SO Journal of Pharmaceutical and Biomedical Analysis (2003), 33(4), 563-570
CODEN: JPBADA; ISSN: 0731-7085
PB Elsevier Science B.V.
DT Journal
LA English
AB Two samples of an anticancer prodrug, AQ4N, were submitted for HPLC assay and showed an unidentified impurity that eluted as a rider' on the tail of the main peak. Math. derivatization of the chromatograms offered several advantages over conventional skimmed integration. A combination of the second derivative amplitude and simple linear regression gave a novel method for estimating the true peak area of the impurity peak. All the calcn. steps were carried out using a widely available spreadsheet program.
IT **136470-65-0**
RL: ANT (Analyte); ANST (Analytical study)
(determination of AQ4N cancer drug by HPLC)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



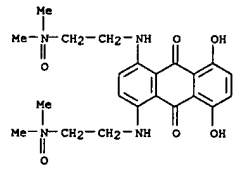
RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN APPLICANT
AN 2003:757670 CAPLUS
DN 139:281237
TI Formulations of anthraquinone derivatives
IN Denny, William Alexander; Patterson, Laurence Hylton; Halbert, Gavin William; Ford, Steven John
PA BTG International Limited, UK
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

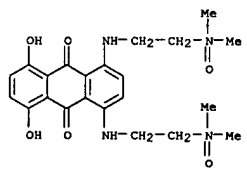
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003078387	A1	20030925	WO 2003-GB1110	20030317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2478867	AA	20030925	CA 2003-2478867	20030317
EP 1485349	A1	20041215	EP 2003-708354	20030317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005256188	A1	20051117	US 2004-507483	20040927
PRAI GB 2002-6255	A	20020315		
US 2002-412776P	P	20020924		
WO 2003-GB1110	W	20030317		

OS MARPAT 139:281237
AB An anthraquinone derivative is formulated so that upon dissoln. in aqueous solution the pH of the solution is in the range of 5 to 9. The compound may be in the form of salt with a physiol. acceptable acid having a pKa in the range of -3.0 (minus 3.0) to 9.0. For example, to 10 mg of an anthracenedione derivative AQ4N, dissolved in 1 mL of MeOH, 73.7 mg of pimelic acid, dissolved in 1 mL of MeOH, was added to yield 8.2 mg (47%) of AQ 4N dipimelate. Also, an anthraquinone derivative AQMN had a cytotoxicity which is at least 5 times greater than that of AQ 4N in the P388 system.
IT **136470-65-0**, AQ 4N
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation and properties of anthraquinone derivs. and their organic acid salts)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



IT **252979-56-9**
RL: PRP (Properties); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation and properties of anthraquinone derivs. and their organic acid salts)
RN 252979-56-9 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, dihydrochloride (9CI) (CA INDEX NAME)



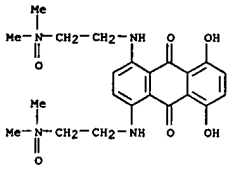
●2 HCl

IT **603961-65-5P 603961-66-6P 603961-67-7P**
603961-68-8P 603961-69-9P 603961-70-2P
603961-71-3P 603961-72-4P 603961-73-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and properties of anthraquinone derivs. and their organic acid salts)
RN 603961-65-5 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, dibenzenesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

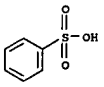
CRN 136470-65-0
CMF C22 H28 N4 O6

L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



CM 2

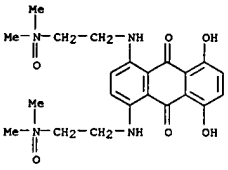
CRN 98-11-3
CMF C6 H6 O3 S



RN 603961-66-6 CAPLUS
CN Acetic acid, dichloro-, compd. with 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione (2:1) (9CI) (CA INDEX NAME)

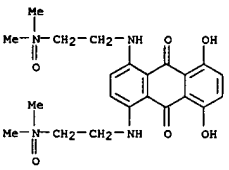
CM 1

CRN 136470-65-0
CMF C22 H28 N4 O6



L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

CRN 136470-65-0
CMF C22 H28 N4 O6



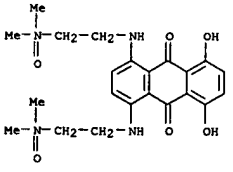
CM 2

CRN 141-82-2
CMF C3 H4 O4

RN 603961-69-9 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, (2R,3R)-2,3-dihydroxybutanedioate (1:2) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 136470-65-0
CMF C22 H28 N4 O6



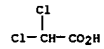
CM 2

CRN 87-69-4
CMF C4 H6 O6

L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

CM 2

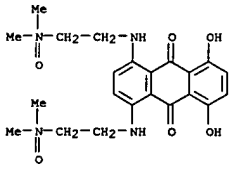
CRN 79-43-6
CMF C2 H2 Cl2 O2



RN 603961-67-7 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, (2Z)-2-butenedioate (1:2) (salt) (9CI) (CA INDEX NAME)

CM 1

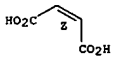
CRN 136470-65-0
CMF C22 H28 N4 O6



CM 2

CRN 110-16-7
CMF C4 H4 O4

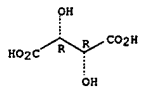
Double bond geometry as shown.



RN 603961-68-8 CAPLUS
CN Propanedioic acid, compd. with 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione (2:1) (9CI) (CA INDEX NAME)

CM 1

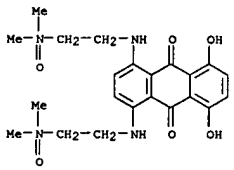
L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.



RN 603961-70-2 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, 2-hydroxy-1,2,3-propanetricarboxylate (1:2) (salt) (9CI) (CA INDEX NAME)

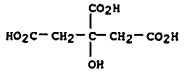
CM 1

CRN 136470-65-0
CMF C22 H28 N4 O6



CM 2

CRN 77-92-9
CMF C6 H8 O7

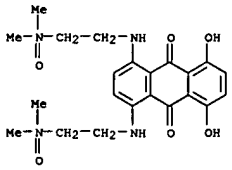


RN 603961-71-3 CAPLUS
CN Propanoic acid, 2-hydroxy-, compd. with 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione (2:1) (9CI) (CA INDEX NAME)

CM 1

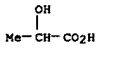
CRN 136470-65-0
CMF C22 H28 N4 O6

L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



CM 2

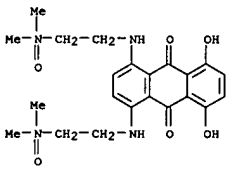
CRN 50-21-5
CMF C3 H6 O3



RN 603961-72-4 CAPLUS
CN Heptanedioic acid, compd. with 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-9,10-anthracenedione (2:1) (9CI) (CA INDEX NAME)

CM 1

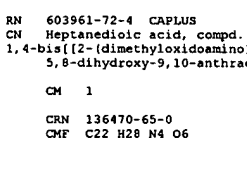
CRN 136470-65-0
CMF C22 H28 N4 O6



CM 2

CRN 111-16-0
CMF C7 H12 O4

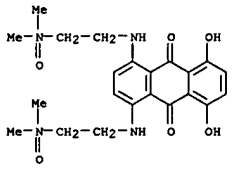
L4 ANSWER 9 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 603961-73-5 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, diacetate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 136470-65-0
CMF C22 H28 N4 O6



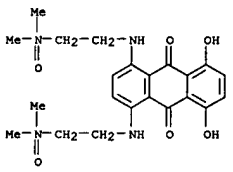
CM 2

CRN 64-19-7
CMF C2 H4 O2

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:957738 CAPLUS
DN 139:46512
TI Bioreductive GDEPT using cytochrome P450 3A4 in combination with AQ4N
AU McCarthy, Helen O.; Yakkundi, Anita; McErlane, Verna; Hughes, Clara M.; Keilty, Gillian; Murray, Margaret; Patterson, Laurence H.; Hirst, David G.; McKeown, Stephanie R.; Robson, Tracy
CS School of Biomedical Sciences, Radiation Science Research Group, University of Ulster at Jordanstown, Newtownabbey, County Antrim, UK
SO Cancer Gene Therapy (2003), 10(1), 40-48
CODEN: CGTHEG; ISSN: 0929-1903
PB Nature Publishing Group
DT Journal
LA English
AB The bioreductive drug, AQ4N, is metabolized under hypoxic conditions and has been shown to enhance the antitumor effects of radiation and chemotherapy drugs. We have investigated the role of cytochrome P 450 3A4 (CYP3A4) in increasing the metabolism of AQ4N using a gene-directed enzyme prodrug therapy (GDEPT) strategy. RIF-1 murine tumor cells were transfected with a mammalian expression vector containing CYP3A4 cDNA. In vitro AQ4N metabolism, DNA damage, and clonogenic cell kill were assessed following exposure of transfected and parental control cells to AQ4N. The presence of exogenous CYP3A4 increased the metabolism of AQ4N and significantly enhanced the ability of the drug to cause DNA strand breaks and clonogenic cell death. Cotransfection of CYP reductase with CYP3A4 showed a small enhancement of the effect in the DNA damage assay only. A single injection of CYP3A4 into established RIF-1 murine tumors increased the metabolism of AQ4N, and when used in combination with radiation, three of nine tumors were locally controlled for °60 days. This is the first demonstration that CYPs alone can be used in a GDEPT strategy for bioredn. of the cytotoxic prodrug, AQ4N. AQ4N is the only CYP-activated bioreductive agent in clin. trials. Combination with a GDEPT strategy may offer a further opportunity for targeting radiation-resistant and chemo-resistant hypoxic tumor cells.
IT 136470-65-0, AQ4N
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioreductive GDEPT using cytochrome P 450 3A4 in combination with AQ4N)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

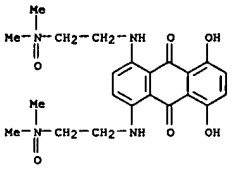
L4 ANSWER 10 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

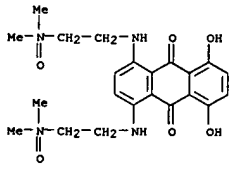
L4 ANSWER 11 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:733727 CAPLUS
DN 138:296878
TI Bioreductively activated antitumor N-oxides: the case of AQ4N, a unique approach to hypoxia-activated cancer chemotherapy
AU Patterson, Laurence H.
CS Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, University of London, London, WC1N 1AX, UK
SO Drug Metabolism Reviews (2002), 34(3), 581-592
CODEN: DMTRAR; ISSN: 0360-2532
PB Marcel Dekker, Inc.
DT Journal; General Review
LA English
AB A review. Aliphatic amine N-oxides have long been identified as non-toxic metabolites of a large number of tertiary amine drugs. Bioredn. of such N-oxides will generate the active parent amine. This principle has been adopted to develop AQ4N, a di-N-oxide anticancer prodrug with little intrinsic cytotoxicity. However, AQ4N is bioreduced in hypoxic regions of solid tumors and micro-metastatic deposits to generate a cytotoxic alkylaminoanthraquinone metabolite. The 4-electron reduction metabolite of AQ4N has high affinity for DNA and is a potent inhibitor of topoisomerase II, a DNA processing enzyme crucial to cell division. The development of AQ4N has proceeded on many fronts in order to establish this unique anticancer prodrug opportunity. Preclin. studies in vivo have demonstrated that although AQ4N has little or no intrinsic cytotoxic activity per se it (i) enhances the antitumor effects of radiation and conventional chemotherapeutic agents, (ii) is pharmacokinetically stable, and (iii) is a substrate for cytochrome P 450 (CYP). A study of AQ4N metabolism in vitro and ex vivo using purified CYP enzymes, phenotyped human livers and CYP transfected cell lines shows that CYP3A, 1A and 1B1 family members contribute to AQ4N bioredn. in the absence of oxygen. Importantly AQ4N is shown to be metabolized by tumors known to express CYP isoforms. AQ4N is currently in Phase I clin. trials.
IT **136470-65-0**, AQ4N
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prodrug; bioreductively activated antitumor N-oxides and the case of AQ4N as a unique approach to hypoxia-activated cancer chemotherapy)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 11 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:696717 CAPLUS
DN 136:379563
TI The chemopotentiation of cisplatin by the novel bioreductive drug AQ4N
AU Gallagher, R.; Hughes, C. M.; Murray, M. M.; Friery, O. P.; Patterson, L. H.; Hirst, D. G.; McKeown, S. R.
CS Radiation Science Research Group, School of Biomedical Sciences, University of Ulster at Jordanstown, Newtownabbey, BT37 0QB, UK
SO British Journal of Cancer (2001), 85(4), 625-629
CODEN: BJCAAI; ISSN: 0007-0920
PB Harcourt Publishers Ltd.
DT Journal
LA English
AB AQ4N is a bioreductive drug that can significantly enhance the antitumor effect of radiation and cyclophosphamide. The aim of this study was to examine the ability of AQ4N to potentiate the antitumor effect of cisplatin and to compare it to the chemopotentiation effect of tirapazamine. In the T50/80 murine tumor model, AQ4N (50-100 mg/kg) was administered 30 min, 2.5 h, or 6 h prior to cisplatin (4 or 8 mg/kg); this produced an antitumor effect that was .apprx.1.5-2 times greater than that achieved by a single 4 or 8 mg/kg dose of cisplatin. Tirapazamine (25 mg/kg) administered 2.5 h prior to cisplatin (4 mg/kg) resulted in a small increase in antitumor efficacy. AQ4N was also successful in enhancing the antitumor effect of cisplatin in the SCCVII and RIF-1 murine tumor models. This resulted in an increased cell kill of >3 logs in both models; this was a greater cell kill than that observed for tirapazamine with cisplatin. Combination of cisplatin with AQ4N or tirapazamine resulted in no addnl. bone marrow toxicity compared to cisplatin administered alone. In conclusion, AQ4N has the potential to improve the clin. efficacy of cisplatin.
IT **136470-65-0**, AQ4N
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chemopotentiation of cisplatin by AQ4N)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

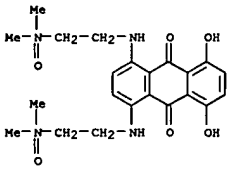


RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

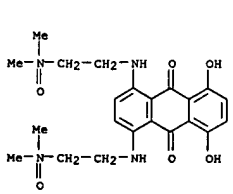
L4 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:266493 CAPLUS
DN 135:174632
TI A preclinical pharmacokinetic study of the bioreductive drug AQ4N
AU Loadman, P. M.; Swaine, D. J.; Bibby, M. C.; Welham, K. J.; Patterson, L. H.
CS Cancer Research Unit, University of Bradford, Bradford, BD7 1DP, UK
SO Drug Metabolism and Disposition (2001), 29(4, Pt. 1), 422-426
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB AQ4N (1,4-bis-{[2-(dimethylamino-N-oxide)ethyl]amino}5,8-dihydroxyanthracene-9,10-dione) is in a class of bioreductive agents incorporating the aliphatic N-oxide functionality and is well documented as a very effective enhancer of radiotherapy and chemotherapy. The compound is shortly to enter Phase I clin. trials in the United Kingdom, and this study describes the preclin. pharmacokinetics and metabolism of AQ4N in mice. AQ4N was administered by i.v. injection at doses of 200, 100, and 20 mg/kg and was quantified by high-performance liquid chromatog. and liquid chromatog./mass spectroscopy. There was a linear increase in the maximum plasma concentration (Cmax) proportional to dose with a Cmax of 1171 μg/mL at the maximum tolerated dose of 200 mg/kg. The area under plasma concentration vs. time curve (AUC) increased disproportionately with dose from 14.1 μg/h/mL at 20 mg/kg to 247 μg/h/mL at 200 mg/kg with a subsequent decrease in clearance. Terminal elimination half-lives ranged from 0.64 to 0.83 h. The spectra of the two major metabolites matched those from authentic stds. with the mol. ions [M + H]+ being detected at m/z 445.4 (AQ4N), m/z 429.5 (AQ4 mono-N-oxide) and m/z 413.5 (AQ4). Only low concns. of the toxic metabolite (AQ4) were detected in plasma at all 3 doses, with the AUC and Cmax at 200 mg/kg being 3.54 μg/h/mL and 3.7 μg/mL, resp., representing <2% of AQ4N. Concns. of the intermediate AQ4 M represented 8, 10, and 18% of those for AQ4N at the doses of 20,100, and 200 mg/kg. The concns. necessary for a therapeutic response in vivo have been described in this pharmacokinetic study.
IT 136470-65-0, AQ4N
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preclin. pharmacokinetics of the bioreductive drug AQ4N)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 13 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:41460 CAPLUS
DN 135:86350
TI AQ4N: A new approach to hypoxia-activated cancer chemotherapy
AU Patterson, L. H.; McKeown, S. R.
CS Department of Pharmaceutical and Biological Chemistry, School of Pharmacy, University of London, London, WC1N 1AX, UK
SO British Journal of Cancer (2000), 83(12), 1589-1593
CODEN: BJCAAI; ISSN: 0007-0920
PB Harcourt Publishers Ltd.
DT Journal; General Review
LA English
AB A review, with 29 refs. Preclin. studies demonstrate that in vivo AQ 4N enhances the anti-tumor effects of radiation and chemotherapeutic agents with a dose-modifying factor of approx. 2.0. With careful scheduling no, or very little, addnl. normal tissue toxicity should be observed AQ 4N is a bioreductive prodrug of a potent, stable, reduction product which binds non-covalently to DNA, facilitating antitumor activity in both hypoxic and proximate oxic tumor cells. AQ 4N is clearly different in both its mechanism of action and potential bystander effect compared to previously identified bioreductive drugs. In particular AQ 4N is the only bioreductive prodrug topoisomerase II inhibitor to enter clin. trials. Targeting this enzyme, which is crucial to cell division, may help sensitize tumors to repeated (fractionated) courses of radiotherapy. This is because in principle, the bioredn. product of AQ4N can inhibit the topoisomerase activity of hypoxic cells as they attempt to re-enter the cell cycle.
IT 136470-65-0, AQ 4N
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AQ 4N as new approach to hypoxia-activated cancer chemotherapy)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



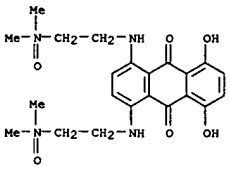
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:725530 CAPLUS
DN 133:303257
TI Solid matrices for surface-enhanced Raman spectroscopy
IN Bell, Steven Ernest John
PA Qubis Ltd., UK
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000059624	A1	20001012	WO 2000-GB1192	20000405
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2000039745	A5	20001023	AU 2000-39745	20000405
	EP 1169120	A1	20020109	EP 2000-918980	20000405
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 2003149153	A1	20030807	US 2002-958225	20020111
	US 6649683	B2	20031118		
PRAI	GB 1999-7688	A	19990406		
	WO 2000-GB1192	W	20000405		

AB Methods of forming a solid matrix for use with surface-enhanced Raman spectroscopy (SERS) are described which entail mixing a colloidal metal solution with a polymeric support medium to form a suspension; optionally depositing the suspension on a surface; and then drying the suspension to form the matrix. The polymeric support medium provides a polymer/sol suspension in which the sol particles are resistant to aggregation and precipitation Upon drying the suspension shrinks to provide a mech.-hard film subsequently usable to provide a sample for spectroscopic anal. Solid matrixes comprising metal particles and a polymeric support medium for use in SERS are also described, as is their use in SERS.
IT 136470-65-0, AQ4N
RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
(solid matrixes comprising metal particles and polymeric support media for surface-enhanced Raman spectroscopy and their preparation and use)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

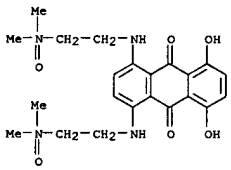
L4 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:444226 CAPLUS
DN 133:305336
TI Enhancement of chemotherapy and radiotherapy of murine tumors by AQ4N, a bioreductively activated anti-tumor agent
AU Patterson, L. H.; McKeown, S. R.; Ruparelia, K.; Double, J. A.; Bibby, M. C.; Cole, S.; Stratford, I. J.
CS School of Pharmacy and Pharmaceutical Sciences, De Montfort University, Leicester, LE1 9BH, UK
SO British Journal of Cancer (2000), 82(12), 1984-1990
CODEN: BJCAAI; ISSN: 0007-0920
PB Harcourt Publishers Ltd.
DT Journal
LA English
AB AQ4 (1,4-Bis-{[2-(dimethylamino-N-oxide)ethyl]amino}5,8-dihydroxyanthracene-9, 10-dione) is a prodrug designed to be excluded from cell nuclei until bioreduced in hypoxic cells to AQ4, a DNA intercalator and topoisomerase II poison. Thus, AQ4N is a highly selective bioreductive drug that is activated in, and is preferentially toxic to, hypoxic cells in tumors. Five murine tumors (MAC16, MAC26, NT, SCCVII and RIF-1) have been used to investigate the anti-tumor effects of AQ4N. In only one tumor (MAC16) was AQ4N shown to be active as a single agent. However, when combined with methods to increase the hypoxic tumor fraction in RIF-1 (by phys. clamping) and MAC26 tumors (using hydralazine) there was a substantial enhancement in anti-tumor effect. Notably, RIF-1 tumors treated with AQ4N (250 mg kg-1) followed 15 min later by phys. occluding the blood supply to the tumor for 90 min, resulted in a 13-fold increase in growth delay. When combined with radiation or chemotherapy, AQ4N substantially increased the effectiveness of these modalities in a range of in vivo model systems. AQ4N potentiates the action of radiation in both a drug and radiation dose-dependent manner. Further the enhancement observed is schedule-independent with AQ4N giving similar effects when given at any time within 16 h before or after the radiation treatment. In combination with chemotherapy it is shown that AQ4N potentiates the activity of cyclophosphamide, cisplatin and thiotepa. Both the chemotherapeutic drugs and AQ4N are given at doses which individually are close to their estimated maximum tolerated dose (data not included) which provides indirect evidence that in the combination chemotherapy expts. there is some tumor selectivity in the enhanced action of the drugs.
IT **136470-65-0**, AQ4N
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of chemotherapy and radiotherapy of murine tumors by AQ4N, a bioreductively activated anti-tumor agent)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

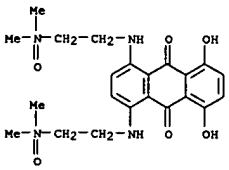
L4 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

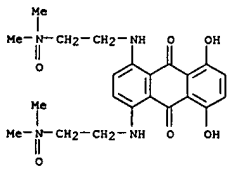
L4 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:377582 CAPLUS
DN 133:144412
TI High-performance liquid chromatographic analysis of AQ4N, an alkylaminoanthraquinone N-oxide
AU Swaine, D. J.; Loadman, P. M.; Bibby, M. C.; Graham, M. A.; Patterson, L. H.
CS Clinical Oncology Unit, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK
SO Journal of Chromatography, B: Biomedical Sciences and Applications (2000), 742(2), 239-245
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier Science B.V.
DT Journal
LA English
AB A simple, highly selective and reproducible reversed-phase high-performance liquid chromatog. method has been developed for the anal. of the new anti-cancer pro-drug AQ4N. The sample pre-treatment involves a simple protein precipitation protocol, using methanol. Chromatog. sepns. were performed using a HiChrom HIRPB (25 cm+4.6 mm I.D.) column, with mobile phase of acetonitrile-ammonium formate buffer (0.05 M) (22:78, volume/volume), with final pH adjusted to 3.6 with formic acid. The flow-rate was maintained at 1.2 mL min-1. Detection was via photodiode array performed in the UV range at 242 nm and, since the compds. are an intense blue color, in the visible range at 612 nm. The structurally related compound mitoxantrone was used as internal standard The validated quantification range of the method was 0.05-10.0 μg ml-1 in mouse plasma. The inter-day relative standard deviations (RSDs) (n=5) ranged from 18.4% and 12.1% at 0.05 μg ml-1 to 2.9% and 3.3% at 10.0 μg ml-1 for AQ4N and AQ4, resp. The intra-day RSDs for supplemented mouse plasma (n=6) ranged from 8.2% and 14.2% at 0.05 μg ml-1 to 7.6% and 11.5% at 10.0 μg ml-1 for AQ4N and AQ4, resp. The overall recovery of the procedure for AQ4N was 89.4±1.77% and 76.1±7.26% for AQ4. The limit of detection was 50 ng ml-1 with a 100 μl sample volume The method described provides a suitable technique for the future anal. of low levels of AQ4N and AQ4 in clin. samples.
IT **136470-65-0**, AQ4N
RL: ANT (Analyte); ANST (Analytical study)
(high-performance liquid chromatog. anal. of AQ4N, alkylaminoanthraquinone N-oxide)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:295136 CAPLUS

DN 133:187613

TI Enhancement of the antitumor effect of cyclophosphamide by the bioreductive drugs AQ4N and tirapazamine

AU Friery, O. P.; Gallagher, R.; Murray, M. M.; Hughes, C. M.; Galligan, E. S.; McIntyre, I. A.; Patterson, L. H.; Hirst, D. G.; McKeown, S. R.

CS Radiation Science Research Group, University of Ulster at Jordanstown, Antrim, BT37 0QB, UK

SO British Journal of Cancer (2000), 82(8), 1469-1473
CODEN: BJCAAI; ISSN: 0007-0920

PB Churchill Livingstone

DT Journal

LA English

AB The ability of the bioreductive drugs AQ4N and tirapazamine to enhance the antitumor effect of cyclophosphamide was assessed in three murine tumor models. In male BDF mice implanted with the T50/80 mammary carcinoma, AQ4N (50-150 mg/kg) in combination with 100 mg cyclophosphamide/kg produced an effect equivalent to that of a single 200-mg/kg dose of cyclophosphamide alone. Tirapazamine (25 mg/kg) in combination with 100 mg cyclophosphamide/kg produced an effect equivalent to that of a single 150-mg/kg dose of cyclophosphamide alone. In C3H mice implanted with the SCCVII or RIF-1 tumors, enhancement of tumor cell killing was found with both drugs in combination with cyclophosphamide (50-200 mg/kg); AQ4N (50-200 mg/kg) produced a more effective combination than tirapazamine (12.5-50 mg/kg). Unlike tirapazamine, which caused a significant increase in toxicity to bone marrow cells, the combination of AQ4N (100 mg/kg) 6 h prior to cyclophosphamide (100 mg/kg) resulted in no addnl. toxicity towards bone marrow cells compared to that caused by cyclophosphamide alone. In conclusion, AQ4N gave a superior antitumor effect compared to tirapazamine when administered with a single dose of cyclophosphamide (100 mg/kg).

IT **136470-65-0**, AQ4N
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of the antitumor effect of cyclophosphamide by the bioreductive drugs AQ4N and tirapazamine)

RN 136470-65-0 CAPLUS

CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 19 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:88266 CAPLUS

DN 132:260303

TI Hypoxia-dependent retinal toxicity of bioreductive anticancer prodrugs in mice

AU Lee, Alan E.; Wilson, William R.

CS Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.

SO Toxicology and Applied Pharmacology (2000), 163(1), 50-59
CODEN: TXAPA9; ISSN: 0041-008X

PB Academic Press

DT Journal

LA English

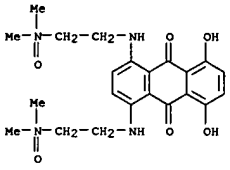
AB The bioreductive anticancer prodrug CI-1010 ((2R)-1-[(2-bromoethyl)amino]-3-(2-nitro-1H-imidazol-1-yl)-2-propanol hydrobromide) is an alkylating nitroimidazole which shows selective toxicity against hypoxic cells in murine tumors, but causes extensive apoptosis in the outer retina in rodents and monkeys. This irreversible retinal toxicity has terminated preclin. development of CI-1010. We have investigated whether such toxicity is due to physiol. hypoxia in the retina, and whether it is a general feature of hypoxia-selective bioreductive drugs. Retinal damage was quantified by morphometric anal. of histol. sections following treatment of female C57Bl6 mice. Both CI-1010 and tirapazamine (TPZ, 1,2,4-benzotriazin-3-amine 1,4-dioxide), a bioreductive drug in Phase III clin. trial, caused a time and dose-dependent loss of photoreceptor cells of the outer retina following administration of single i.p. doses. The lesion caused by TPZ was qual. similar to that with CI-1010, but was less severe at equivalent fractions of the maximum tolerated dose (as defined by lethality). With both bioreductive drugs, lesion severity was increased if animals breathed 10% O2 for 3 h after drug administration, while breathing 95% O2/5% CO2 was protective. Other hypoxia-selective bioreductive drugs tested (the quinone porfiromycin, the anthraquinone N-oxide AQ4N and the nitrogen mustard prodrugs SN 23816 and SN 25341) did not cause retinal damage at their maximum tolerated doses. This study suggests that the retinal toxicity of bioreductive drugs might be avoided by manipulation of tissue hypoxia using 95% O2/5% CO2, although this intervention could suppress antitumor activity. The finding that not all bioreductive drugs cause retinal toxicity suggests this toxicity can be avoided through appropriate drug design. (c) 2000 Academic Press.

IT **136470-65-0**, AQ4N
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoxia-dependent retinal toxicity of bioreductive anticancer prodrugs in mice)

RN 136470-65-0 CAPLUS

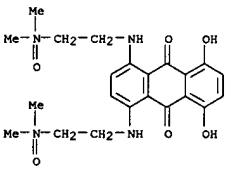
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 19 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



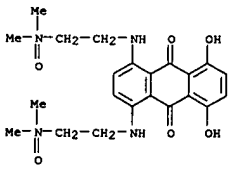
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:84749 CAPLUS
DN 132:122398
TI Preparation of 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione via 3,6-dichlorophthalic anhydride.
IN Denny, William Alexander; Lee, Ho Huat
PA BTG International Limited, UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000005194	A1	20000203	WO 1999-GB2337	19990720
	W: CA, JP, MX, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2337070	AA	20000203	CA 1999-2337070	19990720
	EP 1097125	A1	20010509	EP 1999-934892	19990720
	EP 1097125	B1	20040929		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002521357	T2	20020716	JP 2000-561151	19990720
	AT 277887	E	20041015	AT 1999-934892	19990720
	ES 2226411	T3	20050316	ES 1999-934892	19990720
	US 6320063	B1	20011120	US 2000-736360	20001215
PRAI	GB 1998-15910	A	19980721		
	WO 1999-GB2337	W	19990720		

OS CASREACT 132:122398
AB 1,4-Bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione (I) was prepared by a method which includes the conversion of 3,6-dichlorophthalic anhydride to 3,6-difluorophthalic anhydride. Thus, 3,6-dichlorophthalic anhydride was heated over a layer of KF/NaF at 140-170° and then at 260-270° to give 76% 3,6-difluorophthalic anhydride. The latter was heated with hydroquinone, NaCl, and AlCl3 at 200° to give 98% 1,4-difluoro-5,8-dihydroxyanthracene-9,10-dione. This was stirred with N,N-dimethylethylenediamine in pyridine for 45 h to give 41% I.
IT **136470-65-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione via 3,6-dichlorophthalic anhydride)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 21 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:769512 CAPLUS
DN 132:87720
TI Rat cytochromes P450 (CYP) specifically contribute to the reductive bioactivation of AQ4N, an alkylaminoanthraquinone-di-N-oxide anticancer prodrug
AU Raleigh, S. M.; Wanogho, E.; Burke, M. D.; Patterson, L. H.
CS School of Pharmacy & Pharmaceutical Sciences, De Montfort University, Leicester, LE1 9BH, UK
SO Xenobiotica (1999), 29(11), 1115-1122
CODEN: XENOBH; ISSN: 0049-8254
PB Taylor & Francis Ltd.
DT Journal
LA English
AB The bioreductive activation of the alkylaminoanthraquinone di-N-oxide prodrug AQ4N has been characterized in rat hepatic tissue using HPLC. AQ4N was shown to be metabolized to two products, namely AQM, the two electron reduced mono-N-oxide, and AQ4, the four electron reduced active cytotoxic agent. Metabolism was shown to occur in microsomes with an apparent Km = 30.29 μM and Vmax = 1.05 nmol/mg/min. Bioredn. was dependent on anaerobic conditions and the presence of the reduced cofactor NADPH. Ketoconazole (100 μM) and carbon monoxide both inhibited AQ4N metabolism inferring a role for cytochrome P 450 (CYP). Microsomes from phenobarbitone and isoniazid-pretreated animals significantly ($p < 0.05$) enhanced the formation of AQ4 from AQ4N indicating a role for CYP2B and 2E resp. The involvement of both CYP2B and 2E was confirmed by the use of CYP-specific inhibitors. In conclusion, the involvement of rat hepatic CYP in the reductive bioactivation of the novel antitumor prodrug AQ4N has been established in detail for the first time. These findings highlight an important interspecies difference between the metabolism of AQ4N in rat and man which was shown earlier to be mediated by CYP3A enzymes. The pharmacol. significance of this is discussed.
IT **136470-65-0**, AQ 4N
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(rat CYP2B and CYP2E specifically contribute to reductive bioactivation of alkylaminoanthraquinone-di-N-oxide anticancer prodrug AQ4N in rat microsomes)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

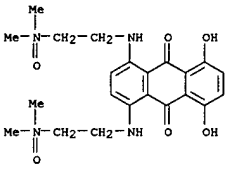


L4 ANSWER 21 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

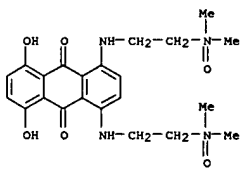
L4 ANSWER 22 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:703964 CAPLUS
DN 132:75438
TI Effects of AQ4N and its reduction product on radiation-mediated DNA strand breakage
AU Mohsin Ali, M.; Symons, M. C. R.; Taiwo, F. A.; Patterson, L. H.
CS Institute of Nuclear Science and Technology, Atomic Energy Research Establishment, Dhaka, Bangladesh
SO Chemico-Biological Interactions (1999), 123(1), 1-10
CODEN: CBINA8; ISSN: 0009-2797
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB Supercoiled plasmid pBR322 DNA was irradiated in phosphate buffer by 60Co γ-rays at a dose rate 19.26 Gy/min and total dose of 10 Gy in the presence of a bioreductive antitumor prodrug namely 1,4-bis [[2-(dimethylamino-N-oxide)ethyl] amino] 5, 8-dihydroxyanthracene-9,10-dione (AQ4N) and its DNA affinic reduction product 1,4-bis[[2-(dimethylamino)ethyl] amino] 5,8-dihydroxyanthracene-9,10-dione (AQ4) under air and nitrogen. AQ4N and AQ4 were found to protect against radiation-induced plasmid single and double strand breakage as assessed by agarose gel electrophoresis. The differences between the two agents, and between atmospheres of air or nitrogen were negligible. It was also found that the protection efficiencies of the compds. were pH dependent and showed maximum protection at pH 6. These results indicate that protection of DNA by AQ4 and AQ4N against radiation damage is an indirect effect since both agents are equally effective despite major differences in their DNA affinity. It is likely that radiation-induced phosphate buffer radicals are intercepted by AQ4 and AQ4N in a pH-dependent process.
IT **136470-65-0**, AQ 4N
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AQ4N and its reduction product effect on radiation-mediated DNA strand breakage)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 22 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:605554 CAPLUS
DN 132:49780
TI A large-scale synthesis of the bioreductive drug 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-N-oxide (AQ4N)
AU Lee, Ho H.; Denny, William A.
CS Faculty of Medical and Health Sciences, Auckland Cancer Society Research Centre, The University of Auckland, Auckland, N. Z.
SO Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1999), (19), 2755-2758
CODEN: JCPRB4; ISSN: 0300-922X
PB Royal Society of Chemistry
DT Journal
LA English
AB A large-scale synthesis of the bis-bioreductive drug 1,4-bis[[2-(dimethylamino)ethyl]amino]-5,8-dihydroxyanthracene-9,10-dione bis-N-oxide (AQ4N) has been developed. This six-step synthesis provides AQ4N in 20% overall yield from readily available tetrachlorophthalic anhydride. The key step was a KF-NaF-mediated conversion of 3,6-dichlorophthalic anhydride to 3,6-difluorophthalic anhydride, which could be achieved in 77% yield on a 100 g scale. A trace impurity in AQ4N was determined (by LC-MS and independent synthesis) to be the mono-N-oxide 1-amino-4-[2-(dimethylamino)ethyl]amino-5,8-dihydroxyanthracene-9,10-dione N-oxide. This is formed spontaneously from AQ4N under a number of conditions, including during HPLC on reversed-phase columns.
IT **252979-56-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of bis[[(dimethylamino)ethyl]amino]dihydroxyanthracenedione dioxide)
RN 252979-56-9 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy-, dihydrochloride (9CI) (CA INDEX NAME)

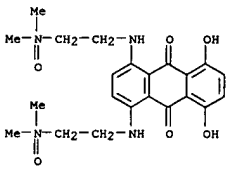


●2 HCl

RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD

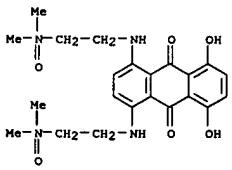
L4 ANSWER 23 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:5867 CAPLUS
DN 130:231829
TI Involvement of human cytochromes P450 (CYP) in the reductive metabolism of AQ4N, a hypoxia activated anthraquinone di-N-oxide prodrug
AU Raleigh, S. M.; Wanogho, E.; Burke, M. Danny; McKeown, S. R.; Patterson, L. H.
CS Department of Pharmaceutical Sciences, De Montfort University, Leicester, LE1 9BH, UK
SO International Journal of Radiation Oncology, Biology, Physics (1998), 42(4), 763-767
CODEN: IOBPD3; ISSN: 0360-3016
PB Elsevier Science Inc.
DT Journal
LA English
AB To establish the role of the human cytochromes P 450 (CYPs) in the reductive metabolism of the novel anthraquinone di-N-oxide prodrug AQ4N. Metabolism of AQ4N was conducted in a panel of 17 human phenotyped liver microsomes. AQ4N and metabolites were detected by reverse phase isocratic HPLC. CYP inhibitors and Spearman rank correlation were used to determine the significance of AQ4N metabolism vs. specific CYP activity and/or expression. Anaerobic metabolism of AQ4N to the 2-electron reduction product, AQM, and the 4-electron reduced tertiary amine, AQ4, occurred in all 17 human liver microsome prepns. The range (± SE) for total AQ4N turnover was 14.26±1.43 nmol/incubate (highest) to 3.65±1.05 nmol/incubate (lowest). Metabolism was not detected in the absence of NADPH or microsomes. In aerobic incubates, AQM was less than 4% of anaerobic values whereas AQ4 was undetectable. CYP-mediated metabolism of AQ4N was inhibited completely by ketoconazole (KET) and carbon monoxide (CO), two global inhibitors of CYP-mediated metabolism AQ4N metabolism correlated significantly with probes for CYP 3A, specifically benzoxylresorufin O-dealkylation [r(s) = 0.70, p <0.01] and tamoxifen N-demethylation (r(s) = 0.85, p < 0.01), but not with probes for CYPs 2C, 2D, and 1A. CYP 3A involvement was confirmed by the use of the CYP 3A specific inhibitor, triacetyloleandomycin (TAO), which repressed the formation of AQM to 13% of the uninhibited value and abolished completely the formation of AQ4. Alpha-naphthoflavone (ANF), an inhibitor of CYP 2C and 1A, had no significant effect on AQ4N metabolism These data suggest that the human CYP 3A enzymes can contribute to the reductive metabolism of AQ4N. CYP 3A enzymes are highly expressed in a broad spectrum of human cancers. The results show that AQ4N requires anaerobic conditions for CYP 3A-mediated reduction and hence this subfamily of enzymes is likely to selectively activate AQ4N in hypoxic tumors.
IT **136470-65-0**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(human cytochromes P 450 (CYP) in reductive metab. of AQ4N, a hypoxia activated anthraquinone di-N-oxide prodrug)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



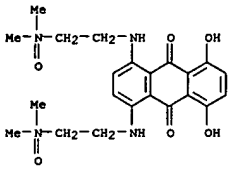
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:262040 CAPLUS
DN 127:60340
TI DNA topoisomerase II-dependent cytotoxicity of alkylaminoanthraquinones and their N-oxides
AU Smith, Paul J.; Blunt, Nicola J.; Desnoyers, Rodwige; Giles, Yvonne; Patterson, Laurence H.
CS College Medicine, University Wales, Cardiff, CF4 4XN, UK
SO Cancer Chemotherapy and Pharmacology (1997), 39(5), 455-461
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer
DT Journal
LA English
AB The role of DNA topoisomerase II (TI II) was studied in the biol. actions of a series of novel alkylaminoanthraquinones. The agents based on the anticancer TI II poison mitoxantrone, included AQ4 and AQ6, together with the corresponding mono-N-oxide (AQ6NO) and di-N-oxide (AQ4NO). The R3N+-O- modification renders the terminal nitrogen group elec. neutral and reduced AQ6NO or abolished AQ4NO-DNA binding. The inhibition of TI II decatenation activity ranked according to DNA-binding capacity. Drug-induced DNA-protein crosslinking in intact cells showed similar ranking, depending upon TI II availability. Inhibition of DNA synthesis in S-phase synchronized cultures ranked in the order of AQ6 > mitoxantrone >> AQ6NO and was independent of TI II availability. Cytotoxicity of acute 1-h exposures for all agents except the inactive AQ4NO was enhanced in a TI II-overproducing cell line.
IT **136470-65-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA topoisomerase II-dependent cytotoxicity of alkylaminoanthraquinones and their N-oxides)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



L4 ANSWER 26 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:79693 CAPLUS
DN 126:139430
TI Flow-cytometric analysis and confocal imaging of anticancer alkylaminoanthraquinones and their N-oxides in intact human cells by 647-nm krypton laser excitation
AU Smith, Paul J.; Desnoyers, Rodwige; Blunt, Nicola; Giles, Yvonne; Patterson, Laurence H.; Watson, James V.
CS MRC Clinical Oncology and Radiotherapeutics Unit, Cambridge, UK
SO Cytometry (1997), 27(1), 43-53
CODEN: CYTODQ; ISSN: 0196-4763
PB Wiley-Liss
DT Journal
LA English
AB Flow cytometry and laser-scanning confocal fluorescence microscopy were used to study the pharmacodynamics, in single intact cells, of 2 novel alkylaminoanthraquinones (AQ4 and AQ6), structurally based on the mid-red-excitable but very weakly fluorescent anticancer agent mitoxantrone, and their resp. N-oxide derivs. (AQ4NO and AQ6NO). The rationale was that N-oxide modifications generate prodrug forms suitable for selective bioreductive activation in hypoxic tumor cells. DNA binding ranked in the order mitoxantrone > AQ6 > AQ4 > AQ6NO » AQ4NO. With both cytometric methods a similar ranking was found for whole-cell and nuclear location of the compds. in human transformed fibroblasts. However, AQ6 had greater nuclear uptake than mitoxantrone, in keeping with its greater capacity to inhibit DNA synthesis. Partial charge neutralization by N-oxide derivatization resulted in loss of DNA synthesis inhibition but retention of the ability to accumulate in the cytosol, an important property for prodrug development. Thus, both flow cytometry and confocal imaging revealed biol. significant differences among the analogs with respect to subcellular distribution and retention. The study demonstrates the potential for these complementary 647-nm krypton laser line-based fluorometric methods to provide relevant structure-activity information in anthraquinone drug-design programs.
IT **136470-65-0**
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(flow-cytometric anal. and confocal fluorescence microscopy of anticancer alkylaminoanthraquinones and their N-oxides in intact human cells)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

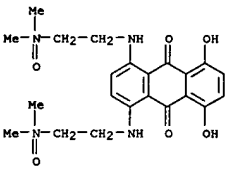
L4 ANSWER 26 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

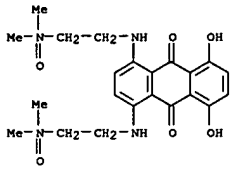
L4 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:492687 CAPLUS
DN 125:211931
TI Tertiary amine N-oxides as bioreductive drugs: DACA N-oxide, nitracrine N-oxide and AQ4N
AU Wilson, WR; Denny, WA; Pullen, SM; Thompson, KM; Li, AE; Patterson, LH; Lee, HH
CS Department Pathology, University Auckland, Auckland, N. Z.
SO British Journal of Cancer, Supplement (1996), 74(27), S43-S47
CODEN: BJCSB5; ISSN: 0306-9443
PB Stockton
DT Journal
LA English
AB Tertiary amine N-oxides of DNA intercalators with alkylamino sidechains are a new class of bioreductive drugs. N-oxidation masks the cationic charge of the amines, forming prodrugs with low DNA binding affinity and low toxicity which can be activated selectively by metabolic reduction under hypoxic conditions. This study compares three intercalator N-oxides (NC-NO, DACA-NO and AQ4N), which, resp., give nitracrine (NC), DACA and AQ4 on reduction In aerobic cell culture all three N-oxides were much less toxic than the corresponding amines, and showed large increases in cytotoxicity under hypoxia. The topoisomerase poisons DACA and AQ4 (and their N-oxides) were less active against non-cycling than cycling cells. However, only AQ4N was active against the mouse mammary tumor MDAH-MCa-4. This dialkylaminoanthraquinone-di-N-oxide has activity at least as great as the reference bioreductive drug RB 6145 against this tumor, both with and without radiation and when combined with the tumor blood flow inhibitor 5,6-dimethylxanthenone-4-acetic acid (DMXAA). It is suggested that the high in vivo activity of AQ4N relative to the other topoisomerase-targeted N-oxide, DACA-NO, may be in part due to release in hypoxic cells of an intracalator with sufficiently high DNA binding affinity that it is retained long enough to kill non-cycling cells when they eventually re-enter the cell cycle.
IT **136470-65-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of tertiary amine N-oxides under aerobic and hypoxic conditions)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



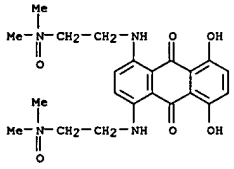
L4 ANSWER 28 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:166048 CAPLUS
DN 124:278232
TI DNA damage following combination of radiation with the bioreductive drug AQ4N: Possible selective toxicity to oxic and hypoxic tumor cells
AU Hejmadi, M. V.; McKeown, S. R.; Friery, O. P.; McIntyre, I. A.; Patterson, LH; Hirst, DG
CS School Biomedical Sciences, University Ulster, Jordanstown, BT37 0QB, Ire.
SO British Journal of Cancer (1996), 73(4), 499-505
CODEN: BJCAAI; ISSN: 0007-0920
PB Stockton
DT Journal
LA English
AB AQ4N (1,4-bis-[[2-(dimethylamino-N-oxide)ethyl]amino]5,8-dihydroxyanthracene-9,10-dione) is a novel bioreductive agent that can be reduced to a stable, DNA-affinic compound, AQ4. The alkaline comet assay was used to evaluate DNA damage induced by AQ4N and radiation. Cells prepared from freshly excised T50/80 murine tumors were shown to have the ability to reduce AQ4N to a DNA-damaging agent; this had disappeared within 24 h of excision. When T50/80 tumors implanted in BDF mice were exposed to radiation in vivo a considerable amount of DNA damage was present in tumors excised immediately. Minimal levels of DNA damage were detectable in tumors excised after 2-5 h. AQ4N given 30 min before radiation had no appreciable influence on this effect and AQ4N alone caused only a small amount of damage. When AQ4N and radiation were combined an increasing number of damaged cells were seen in tumors excised 24-96 h after irradiation This was interpreted as evidence of the continued presence of AQ4, or AQ4-induced damage, which was formed in cells hypoxic at the time of administration of AQ4N. AQ4, a potent topoisomerase II inhibitor, would be capable of damaging cells recruited into the cell cycle following radiation damage to the well-oxygenated cells of the tumor. The kinetics of the expression of the DNA damage is consistent with this hypothesis and shows that AQ4 has persistent activity in vivo.
IT 136470-65-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA damage following combination of radiation with the bioreductive drug AQ4N: possible selective toxicity to oxic and hypoxic tumor cells)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 28 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L4 ANSWER 29 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:798132 CAPLUS
DN 123:275331
TI AQ4N: An alkylaminoanthraquinone N-oxide showing bioreductive potential and positive interaction with radiation in vivo
AU McKeown, S R.; Hejmadi, M V.; McIntyre, I A.; McAleer, J J A.; Patterson, L H.
CS School Biomedical Sciences, University Ulster, BT37 0QB, UK
SO British Journal of Cancer (1995), 72(1), 76-81
CODEN: BJCAAI; ISSN: 0007-0920
PB Macmillan Scientific & Medical Division
DT Journal
LA English
AB AQ4N (1,4-bis-[[2-(dimethylamino-N-oxide)ethyl]amino]5,8-dihydroxy-anthracene-9,10-dione) is a novel alkylaminoanthraquinone N-oxide which, on reduction, forms a stable DNA affinic cytotoxic compound AQ4. The in vivo anti-tumor efficacy of AQ4N was investigated in B6D2F1 mice bearing the T50/80 mammary carcinoma. The effect of the drug was evaluated in combination with hypobaric hypoxia and with radiation (single and multiple fractions). Systemic toxicity was assessed by weight loss post treatment. This was low for AQ4N and was less than that obtained with the bioreductive drugs, RSU 1069 (1-[3-aziridinyl-2-hydroxypropyl]-2-nitroimidazole) and SR 4233 (Tirapazamine, 3-amino-1,2,4-benzotriazine-1,4-dioxide). The anti-tumor effect of AQ4N was potentiated in vivo by combination with hypobaric hypoxia with a dose enhancement ratio of 5.1. This is consistent with the proposal that AQ4N was reduced in vivo to AQ4, resulting in enhanced anti-tumor toxicity. When AQ4N (200 mg kg-1) was combined with single dose radiation (12 Gy) the drug was shown to have an additive interaction with radiation. This was obtained even if the drug was administered from 4 days before to 6 h after radiation treatment. Equivalent anti-tumor activity was also shown when both AQ4N (200 mg kg-1) and radiation (5 + 3 Gy) were administered in fractionated schedules. In conclusion, AQ4N shows significant potential as a bioreductive drug for combination with fractionated radiotherapy.
IT 136470-65-0
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(AQ4N as alkylaminoanthraquinone N-oxide showing bioreductive potential and pos. interaction with radiation in vivo)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

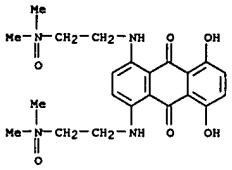
L4 ANSWER 29 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



L4 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:22888 CAPLUS
DN 120:22888
TI Rationale for the use of aliphatic N-oxides of cytotoxic anthraquinones as
prodrug DNA binding agents: a new class of bioreductive agent
AU Patterson, Laurence H.
CS Sch. App. Sci., De Montfort Univ., The Gateway/Leicester, LE1 9BH, UK
SO Cancer and Metastasis Reviews (1993), 12(2), 119-34
CODEN: CMREDA; ISSN: 0167-7659
DT Journal; General Review
LA English
AB A review with 91 refs. NAD(P)H dependent cytochrome P 450's and other hemoproteins under hypoxia, mediate two-electron reduction of a wide range of
structurally dissimilar N-oxides to their resp. tertiary amines. Metabolic reduction can be utilized, in acute and chronic hypoxia, to convert
N-oxides of DNA affinic agents to potent and persistent cytotoxins. In this respect a knowledge of N-oxide bioredn. and the importance of the cationic nature of agents that bind to DNA by intercalation can be combined to rationalize N-oxides as pro-drugs of DNA binding agents. The concept is illustrated using the alkylaminoanthraquinones which are a group of cytotoxic agents with DNA binding affinity that is dependent on the cationic nature of these compds. The actions of the alkylaminoanthraquinones involve drug intercalation into DNA (and double stranded RNA) and inhibition of both DNA and RNA polymerases and topoisomerase Type I and II. A di-N-oxide analog of mitoxantrone,

1,4-bis[[2-(dimethylamino-N-oxide)ethyl]amino]5,8-dihydroxyanthracene-9,10-dione (AQ4N) has been shown to possess no intrinsic binding affinity for DNA and has low toxicity. Yet in the absence of air AQ4N can be reduced in vitro to a DNA affinic agent with up to 1000-fold increase in cytotoxic
potency. Importantly the reduction product, AQ4, is stable under oxic conditions. Studies in vivo indicate that antitumor activity of AQ4N is manifest under conditions that promote transient hypoxia and/or diminish the oxic tumor fraction. The advantage of utilizing the reductive environment of hypoxic tumors to reduce N-oxides is that, unlike conventional bioreductive agents, the resulting products will remain active even if the hypoxia that led to bioactivation is transient or the active compds., once formed, diffuse away from the hypoxic tumor regions. Furthermore, the DNA affinic nature of the active compds. should ensure their localization in tumor tissue.
IT 136470-65-0
RL: PROC (Process)
(bioredn. of, in hypoxia, for DNA binding, antitumor activity in relation to)
RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

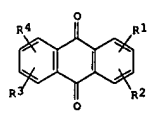
L4 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



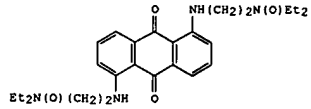
L4 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:582880 CAPLUS
DN 115:182880
TI Preparation of [(dialkylamino)alkylamino]anthraquinone dioxides as neoplasm inhibitors
IN Patterson, Laurence Hylton
PA National Research Development Corp., UK
SO Brit. UK Pat. Appl., 34 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI GB 2237283	A1	19910501	GB 1990-22217	19901012
GB 2237283	B2	19930127		
CA 2038934	AA	19910414	CA 1990-2038934	19901012
CA 2038934	C	20021119		
WO 9105824	A1	19910502	WO 1990-GB1574	19901012
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9065395	A1	19910516	AU 1990-65395	19901012
AU 634125	B2	19930211		
EP 450021	A1	19911009	EP 1990-915322	19901012
EP 450021	B1	19940202		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 04502166	T2	19920416	JP 1990-514278	19901012
JP 2854971	B2	19990210		
ZA 9008178	A	19920624	ZA 1990-8178	19901012
AT 101181	E	19940215	AT 1990-915322	19901012
ES 2062558	T3	19941216	ES 1990-915322	19901012
US 5132327	A	19920721	US 1991-674354	19910410
PRAI GB 1989-23075	A	19891013		
EP 1990-915322	A	19901012		
WO 1990-GB1574	A	19901012		

OS MARPAT 115:182880
GI



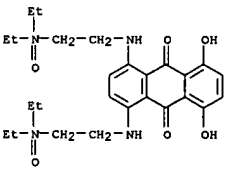
I



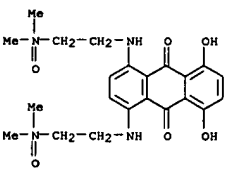
II

AB Title compds. I [R1-R4 = H, X, NHANHR, NHAN(O)R5R6; X = OH, halo, NH2,

L4 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
C1-4 alkoxy, C2-8 alkanoxyloxy; A = C2-4 alkylene; R,R5,R6 = C1-4 alkyl, C2-4 hydroxyalkyl, C2-4 dihydroxyalkyl, or NR5R6 = 3-7 membered heterocyclyl; at least one of R1-R4 = NHAN(O)R5R6, other provisos given], were prepd. Thus, a soln. of 1,5-dichloroanthracene-9,10-dione in 2-(diethylamino)ethylamine was refluxed 4 h and the resulting product was oxidized by MCPBA to give title compd. II. II was active against MCF-7 human breast cancer cells under aerobic and anaerobic conditions.
IT 136470-64-9P 136470-65-0P 136470-66-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as neoplasm inhibitor)
RN 136470-64-9 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(diethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

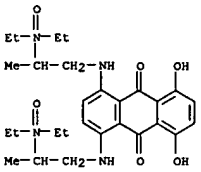


RN 136470-65-0 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(dimethyloxidoamino)ethyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)



RN 136470-66-1 CAPLUS
CN 9,10-Anthracenedione, 1,4-bis[[2-(diethyloxidoamino)propyl]amino]-5,8-dihydroxy- (9CI) (CA INDEX NAME)

L4 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



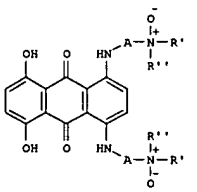
```
=> => d que l11 stat
L5            47 SEA FILE=CAPLUS ABB=ON  PLU=ON  "DENNY WILLIAM ALEXANDER"/AU
L6            54 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("PATTERSON LAURENCE H"/AU OR
                 "PATTERSON LAURENCE HYLTON"/AU)
L7            22 SEA FILE=CAPLUS ABB=ON  PLU=ON  ("HALBERT GAVIN"/AU OR
                 "HALBERT GAVIN W"/AU OR "HALBERT GAVIN WILLIAM"/AU)
L8             2 SEA FILE=CAPLUS ABB=ON  PLU=ON  "FORD STEVEN JOHN"/AU
L9           121 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5 OR L6 OR L7 OR L8
L10           20 SEA FILE=CAPLUS ABB=ON  PLU=ON  L9 AND ANTHRAQUINONE
L11            2 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND FORMULATION


=> d 1-2 bib abs
```

L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:259849 CAPLUS
DN 142:322713
TI **Formulations of anthraquinone** derivatives
IN **Halbert, Gavin William; Ford, Steven John**; Elliott, Moira Alexandra
PA BTG International Limited, UK
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005025537	A1	20050324	WO 2004-GB3954	20040916
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI GB 2003-21787	A	20030917		
GB 2003-29875	A	20031223		

OS MARPAT 142:322713
GI



I

AB A stable, sterile aqueous solution of a compound (I, where A is a C alkylene group with a chain length between NH and N(O)R'R' of at least 2 carbon atoms and R' and R' are each sep. selected from C1-4 alkyl and C2-4 hydroxyalkyl and C2-4 dihydroxyalkyl, or R' and R' together are a C2-6 alkylene), is formulated in a unit dosage form in a sealed container, the solution having a

L11 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:757670 CAPLUS
DN 139:281237
TI **Formulations of anthraquinone** derivatives
IN **Denny, William Alexander; Patterson, Laurence Hylton; Halbert, Gavin William; Ford, Steven John**
PA BTG International Limited, UK
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003078387	A1	20030925	WO 2003-GB1110	20030317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2478867	AA	20030925	CA 2003-2478867	20030317
EP 1485349	A1	20041215	EP 2003-708354	20030317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005256188	A1	20051117	US 2004-507483	20040927
PRAI GB 2002-6255	A	20020315		
US 2002-412776P	P	20020924		
WO 2003-GB1110	W	20030317		

OS MARPAT 139:281237
AB An **anthraquinone** derivative is formulated so that upon dissoln. in aqueous solution the pH of the solution is in the range of 5 to 9. The compound may be in the form of salt with a physiol. acceptable acid having a pKa in the range of -3.0 (minus 3.0) to 9.0. For example, to 10 mg of an anthracenedione derivative AQ4N, dissolved in 1 mL of MeOH, 73.7 mg of pimelic acid, dissolved in 1 mL of MeOH, was added to yield 8.2 mg (47%) of AQ 4N dipimelate. Also, an **anthraquinone** derivative AQMN had a cytotoxicity which is at least 5 times greater than that of AQ 4N in the P388 system.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)
concn. of I up to 150 mg/mL and a pH in the range of 5-9. The soln. may be prepd. without a freeze drying step. **Formulations** of AQ4N were prepd. at 40 mg/mL in 10 mM sodium phosphate buffer at pH 7.0. Effects of freeze drying on the quality of AQ4N product were studied.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> d his full

     (FILE 'HOME' ENTERED AT 10:23:37 ON 29 NOV 2005)

     FILE 'REGISTRY' ENTERED AT 10:23:42 ON 29 NOV 2005
L1              STRUCTURE UPLOADED
                D
L2            0 SEA SSS SAM L1
L3           18 SEA SSS FUL L1

     FILE 'CAPLUS' ENTERED AT 10:24:22 ON 29 NOV 2005
L4           31 SEA ABB=ON  PLU=ON  L3
                D QUE L4 STAT
                D 1-31 BIB ABS HITSTR
                E DENNY WILLIAM/AU
L5           47 SEA ABB=ON  PLU=ON  "DENNY WILLIAM ALEXANDER"/AU
                E PATTERSON LAURENCE/AU
L6           54 SEA ABB=ON  PLU=ON  ("PATTERSON LAURENCE H"/AU OR "PATTERSON
                LAURENCE HYLTON"/AU)
                E HALBERT GAVIN/AU
L7           22 SEA ABB=ON  PLU=ON  ("HALBERT GAVIN"/AU OR "HALBERT GAVIN
                W"/AU OR "HALBERT GAVIN WILLIAM"/AU)
                E FORD STEVEN/AU
L8            2 SEA ABB=ON  PLU=ON  "FORD STEVEN JOHN"/AU
L9          121 SEA ABB=ON  PLU=ON  L5 OR L6 OR L7 OR L8
L10          20 SEA ABB=ON  PLU=ON  L9 AND ANTHRAQUINONE
                D 1-10 TI
                D 3 5
                D 2
                D 2 BIB ABS
L11           2 SEA ABB=ON  PLU=ON  L10 AND FORMULATION
                D QUE L11 STAT
                D 1-2 BIB ABS


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   28 NOV 2005  HIGHEST RN 868827-82-1
     DICTIONARY FILE UPDATES:  28 NOV 2005  HIGHEST RN 868827-82-1

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     ************************************************************
     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
```

****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE CAPLUS

FILE COVERS 1907 - 29 Nov 2005 VOL 143 ISS 23
FILE LAST UPDATED: 28 Nov 2005 (20051128/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

=>